

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

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Appellant:

Beka SOLOMON

Application No. 09/441,140

Filed: November 16, 1999

Appeal No: 2011-009879

PREVENTION OF PROTEIN AGGREGATION

Confirmation No: 3910

Attorney Docket No: SOLOMON1R

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**SUPPLEMENTAL REPLY BRIEF**

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The present supplemental reply brief supplements appellant's reply brief filed May 31, 2011, and is in full accordance with 37 C.F.R. 41.41.

**THE REJECTION OF CLAIMS 177, 210-213, 215-217, 219-223 AND 225-227 UNDER 35 U.S.C. §103 AS BEING UNPATENTABLE OVER WALKER, AS EVIDENCED BY HANAN AND BACSKAI, AND IN VIEW OF BECKER**

**A. Claims 177, 210-213, and 219-223 Should be Considered Independently of Claims 215-217 and 225-227 for the Purpose of This Rejection**

Appellant stated in his main brief on appeal at page 29, that, for the purpose of this rejection, claims 177, 210-213, and 215-217 were considered to stand or fall together while claims 219-223 and 225-227 were considered to be separately patentable and, while standing or falling together, should be considered independently of the first group of claims.

Now, due to the arguments made for the first time in the examiner's answer in the appeal of divisional application no. 11/358,951, appellant will be separately arguing claims 215-217 and 225-227 in this brief. Accordingly, please take note that the following four groups of claims should each be considered separately. First are claims 177 and 210-213. Second are claims 215-217. Third are claims 219-223. Fourth are claims 225-227. While the claims within each of these four groups are considered to stand or fall together, each of

the groups should be independently considered for the purpose of this rejection.

The arguments that are specific to claims 219-223 and 225-227 are presented in appellant's main brief on appeal, properly listed by a separate subheading. The distinction between claims 117, 210-213 and 219-223, on the one hand, and 215-217 and 225-227, on the other hand, will be addressed below, under appropriately identified sub-headings.

**B. The Showing of Unexpected Results is Commensurate in Scope with the Breadth of All of Claims 177, 210-213, 215-217, 219-223 and 225-227**

At pages 43 and 44 of the examiner's answer filed on August 22, 2011, in divisional application 11/358,951, the examiner stated that the evidence of unexpected results relied upon by applicant is not commensurate in scope with the entire range of the claimed invention. The examiner stated that several of the antibodies mentioned by appellant, including 3D6, 12D4, 2C1, 12A11 and 3A1, were not obtained using an immunogen consisting of residues 1-28 of  $\beta$ -amyloid as is required by the claims and therefore fall outside the scope of such claims. This is the first time that the examiner has set forth this interpretation of the claim scope in either the divisional application or this application. As the definition of the antibody in the claims of both the present application and the divisional are very similar, and as the rejections in

both cases are substantially the same, it would be appropriate to respond to this new argument also in the present application.

**1. Argument Applicable to Claims 117, 210-213 and 219-223**

This discussion evidences the examiner's misunderstanding of the scope of the claims. Independent claims 210, 212, 219 and 222 use the language that the monoclonal antibody:

is obtainable using an immunogen  
consisting of a peptide consisting of  
residues 1-28 of beta-amyloid.

The "obtainable" language is intended to encompass antibodies that could be obtained using as an immunogen a peptide consisting of residues 1-28 of  $\beta$ -amyloid, even if the antibody was not so obtained. Thus, for example, if the antibody was obtained using an immunogen consisting of residues 1-7 of  $\beta$ -amyloid, as the epitope of residues 1-7 is also present in the larger peptide of 1-28, one of ordinary skill in the art would expect that antibodies against epitope 1-7 could also be obtained starting with the 1-28 peptide. Thus, such an antibody would be "obtainable using an immunogen consisting of a peptide consisting of residues 1-28 of  $\beta$ -amyloid." One of ordinary skill in the art would not consider that a peptide as large as 28 residues would have only a single epitope

recognized by antibodies. It has a plurality of epitopes and antibodies that recognize any of those epitopes can be raised using the 1-28 peptide, i.e., are "obtainable" using the 1-28 peptide. It would be expected that the same antibodies could also be raised using a smaller peptide encompassing the epitope to which the antibodies bind.

Thus, while antibodies 3D6, 12D4, 2C1, 12A11 and 3A3 were not obtained using an immunogen consisting of  $\beta$ -amyloid residues 1-28, they were obtained by using a peptide within residues 1-28 of  $\beta$ -amyloid and therefore they would also be obtainable using the larger peptide. The examiner has not explained why those antibodies obtained by smaller peptides within 1-28 would not also be obtainable using an immunogen of residues 1-28.

## **2. Argument Applicable to Claims 215-217 and 225-227**

Even if the "obtainable" language is interpreted as meaning "obtained," still, all of the antibodies 3D6, 12B4, 2C1, 12A11 and 3A3 would be considered to fall within the scope of the definition of the antibody appearing in independent claims 215 and 225, i.e., that the monoclonal antibody that:

recognizes an epitope within residues 1-28 of beta-amyloid.

Any antibody raised using residues 1-7 of  $\beta$ -amyloid, for example, will recognize an epitope within residues 1-28 of  $\beta$ -amyloid. There is no reason why the evidence discussed in appellants' reply brief is not commensurate with the scope of claims 215-217 and 225-227.

**3. Argument Applicable to All Claims with Some Noted Distinctions between Claims 210, 212, 219 and 222, and Those Claims Dependent Therefrom, on the One Hand, and Claims 215 and 225, and Those Claims Dependent Therefrom, on the Other Hand**

The antibodies which are used in the method of any of the present claims are defined in the claim as having four specified characteristics. These are (1) being effective to bind  $\beta$ -amyloid; (2) being (a) - for claims 210, 212, 215 and those claims dependent therefrom - effective to inhibit aggregation of  $\beta$ -amyloid in or maintain the solubility of soluble  $\beta$ -amyloid to an extent at least as great as that obtainable with antibody AMY-33, or (b) - for claims 219, 222 and 225 and those claims dependent therefrom - effective to disaggregate the aggregated  $\beta$ -amyloid in said subject; (3) being (a) - for claims 210, 212, 219 and 222 and those claims dependent therefrom - one that is obtainable using an immunogen consisting of a peptide consisting of residues 1-28 of  $\beta$ -amyloid, or (b) - for claims 215 and 225, and those claims dependent therefrom - one that recognizes an epitope within residues 1-28 of  $\beta$ -amyloid, and (4) being (a) - for

claims 210, 219, 215, 225 and those claims dependent therefrom, genetically-engineered, or (b) - for claims 212, 222, and those claims dependent therefrom, being a human monoclonal antibody.

All of antibodies 3D6, 12D4, 2C1, 12A11, 3A2 and 22C8 possess properties (1) to (3). All of them have been shown to have the unexpected property of being able to disaggregate  $\beta$ -amyloid plaque *in vitro*, *ex vivo* and or *in vivo*. Thus, the examiner's arguments about the evidence not being commensurate in scope with the claims are inapplicable with respect to all of the present claims, but especially with respect to claims 215 and 225. As to claims 210, 212, 219 and 222, because each of these antibodies recognize an epitope that exists within residues 1-28 of A $\beta$ , one of ordinary skill in the art would expect that they would be obtainable using a peptide of 1-28 as immunogen. Thus, the evidence is also commensurate in scope with claims 5 and 17.

It is noted that appellant's main brief on appeal stated that a copy of the TABLE summarizing the evidence of record would be attached. It appears that the TABLE was inadvertently not attached to the brief. To correct this error, a copy of the TABLE is attached to the present brief.

The fact that antibody 2H3, which is reported to recognize the epitope of A $\beta$  1-7, was ineffective at preventing

aggregation of soluble  $\beta$ -amyloid does not detract from the evidence of unexpected results. Antibody 2H3 does not fall within the scope of the claims as it does not possess the required attribute (2) as listed above. When determining obviousness under 35 U.S.C. §103, all of the limitations of the claims must be considered and given weight, including limitations that allegedly do not find support in the specification as originally filed. See Manual of Patent Examining Procedure (MPEP) 2143.03(II and *Ex parte Grasselli*, 231 USPQ 393 (Bd. App. 1983) *aff'd mem.* 738 F.2d 453 (Fed. Cir. 1984).

There is no reason to have believed that any antibody that possesses all four of the attributes required by the claims, as discussed above, will not provide unexpected results from anything expected by the combination of references suggested by the examiner. All of the antibodies within the scope of the claims, by definition, must either cause disaggregation of  $\beta$ -amyloid plaque or prevent aggregation of soluble  $\beta$ -amyloid. The fact that the antibodies *per se* will cause disaggregation or prevent aggregation is not obvious from any combination of the references of record and will necessarily provide unexpected results in that the therapeutic effect of the immunotherapeutic allegedly made obvious by the combination of

references will be unexpectedly enhanced by the therapeutic effect of the antibody *per se*, which would have been totally unexpected.

**C. Becker Does Not Create the Expectation that the Naked Antibody 10D5 of Walker would Necessarily be Therapeutically Effective**

**1. Argument Applicable to All Rejected Claims**

At page 45, in the last sentence of the penultimate paragraph, the examiner's answer filed in the appeal of divisional application 11/358,951 states with respect to the rejection of the claims over Walker in view of Becker and others, for the first time, that "the alleged discovery that naked antibodies are therapeutic is merely a reduction to practice of what was explicitly taught by Becker." However, at best, Becker teaches that conformation-specific antibodies that are specific to the  $\beta$ -sheet conformation but do not bind to the random coil or  $\alpha$ -helix conformation of A $\beta$  might be useful "therapeutically." While it has been explained elsewhere that one of ordinary skill in the art would interpret this therapeutic utility as meaning use of the antibody as a delivery tool for therapeutic compounds, even if one were to interpret this term as broadly as the examiner does, it would still not create an expectation that the naked antibody of Walker would be therapeutic. Antibody 10D5 of Walker is not conformationally-specific as it binds both to

the soluble form of A $\beta$  as well as the  $\beta$ -sheet fibril form.

The examiner relies on Hanan and Solomon (1996) for teachings of the inherent properties of the 10D5 antibody. A review of Hanan and Solomon will show that the 10D5 antibody does indeed bind to soluble  $\beta$ -amyloid. Note the second column of page 131 of Hanan and Solomon, lines 9-11, where it states:

The amount of each antibody was sufficient to bind to all soluble  $\beta$ -amyloid peptide (50ng) before first incubation at 37°C.

Clearly, therefore, 10D5 binds to soluble  $\beta$ -amyloid peptide before it is aged at 37°C. Note that Becker itself states that freshly dissolved A $\beta$  is predominantly in the random coil conformation (see column 4, lines 30-31). That monoclonal antibody 10D5 binds to soluble  $\beta$ -amyloid was also known in the prior art as is evidenced by U.S. Patent 6,114,133 to Seubert et al., which is of record in this case. Note column 13, lines 27-39, where it shows that 10D5 bound to  $\beta$ AP<sub>1-28</sub> by ELISA. One of ordinary skill in the art would understand that synthetic  $\beta$ AP<sub>1-28</sub> is not in a  $\beta$ -sheet conformation.

As monoclonal antibody 10D5 binds to both the random coil/ $\alpha$ -helix form of  $\beta$ -amyloid as well as the  $\beta$ -sheet form, it is not an antibody within the scope of Becker and, accordingly, Becker's teachings would disclose nothing to one of ordinary skill in the art about the alleged ability of naked antibody 10D5 to prevent aggregation or cause

disaggregation of  $\beta$ -amyloid plaque. This afterthought of the examiner certainly does not create an expectation that the targeting antibody 10D5 bound to a therapeutic molecule, as allegedly suggested by Walker, would have not only the therapeutic effectiveness of the therapeutic molecule but also the therapeutic effectiveness of the antibody *per se*, which is the subject of the present invention.

Accordingly, the unexpected results established in the present record are of a scope commensurate with scope of the claims for the reasons discussed above and would not have been suggested by Becker. Reversal of the examiner and withdrawal of this rejection is therefore respectfully urged.

### **CONCLUSION**

For all of the reasons presented herein, in conjunction with the reasons explained in appellant's main brief and appellant's original reply brief, reversal of the examiner and withdrawal of all of the rejections of record are earnestly solicited.

Respectfully submitted,

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**SUPPLEMENTAL EVIDENCE APPENDIX**

1. Seubert et al, US 6,114,133, "Methods for Aiding in the Diagnosis of Alzheimer's Disease by Measuring Amyloid- $\beta$  Peptide (X- $\geq$ 41)." This document was cited in IDS filed November 13, 2002, and entered by the examiner in the office action of August 22, 2003.

**TABLE**

| Antibody | Immunogen          | Epitope             | Disaggregate<br><i>In vivo</i> | Disaggregate<br><i>In vitro</i> or<br><i>Ex vivo</i> | Prevention of<br>Aggregation<br><i>In Vitro</i> |
|----------|--------------------|---------------------|--------------------------------|--|---|
| AMY-33   | 1-28 <sup>6</sup>  | ?                   |                                |  | + <sup>2, 6</sup>                               |
| 6C6      | 1-28 <sup>5</sup>  | 3-7 <sup>5</sup>    |                                | + <sup>5, 7</sup>                                    | + <sup>2, 7, 8, 10</sup>                        |
| 10D5     | 1-28 <sup>5</sup>  | 3-6 <sup>11</sup>   | + <sup>1, 3</sup>              | + <sup>5, 11</sup>                                   | + <sup>2, 8, 10</sup>                           |
| 3D6      | 1-5 <sup>4</sup>   | 1-5 <sup>11</sup>   | + <sup>3</sup>                 | + <sup>5, 11</sup>                                   |   |
| 12B4     | 1-42 <sup>5</sup>  | 3-7 <sup>5</sup>    |                                | + <sup>5</sup>                                       |   |
| 2C1      | 1-42 <sup>5</sup>  | 3-7 <sup>5</sup>    |                                | + <sup>5</sup>                                       |   |
| 12A11    | 1-42 <sup>5</sup>  | 3-7 <sup>5</sup>    |                                | + <sup>5</sup>                                       |   |
| 3A3      | 1-42 <sup>5</sup>  | 3-7 <sup>5</sup>    |                                | + <sup>5</sup>                                       |   |
| 22C8     |                    | 3-7 <sup>11</sup>   |                                | + <sup>11</sup>                                      |   |
| 2H3      | 1-12 <sup>4</sup>  | 1-7 <sup>10</sup>   |                                |  | — <sup>2, 8, 10</sup>                           |
| 6E10     |                    | 5-10 <sup>11</sup>  |                                | — <sup>11</sup>                                      |   |
| 14A8     |                    | 4-10 <sup>11</sup>  |                                | — <sup>11</sup>                                      |   |
| 18G11    |                    | 10-18               |                                | — <sup>11</sup>                                      |   |
| 1C2      | 13-28 <sup>7</sup> | 13-28 <sup>7</sup>  |                                | — <sup>7</sup>                                       | — <sup>2, 7, 8</sup>                            |
| 16C11    | 23-42 <sup>5</sup> | 23-42 <sup>5</sup>  | — <sup>3</sup>                 | — <sup>5, 11</sup>                                   |   |
| 266      | 13-28 <sup>4</sup> | 16-24 <sup>11</sup> | — <sup>9</sup>                 | — <sup>5, 11</sup>                                   | — <sup>8</sup>                                  |
| 22D12    | 13-28 <sup>5</sup> | 18-21 <sup>11</sup> |                                | — <sup>5, 11</sup>                                   |   |
| 6F/3D    | 8-17 <sup>6</sup>  |                     |                                |  | — <sup>6</sup>                                  |
| 21F12    | 33-42 <sup>4</sup> | 33-42 <sup>5</sup>  | — <sup>3</sup>                 | — <sup>5, 11</sup>                                   |   |
| 14C2     |                    | 33-40 <sup>7</sup>  |                                | — <sup>7</sup>                                       | — <sup>7</sup>                                  |
| 2G3      | 33-40 <sup>4</sup> |                     |                                | — <sup>11</sup>                                      |   |

<sup>1</sup> Bacskai et al., "Imaging of Amyloid- $\beta$  Deposits in Brains of Living Mice Permits Direct Observation of Clearance of Plaques with Immunotherapy", *Nature Medicine*, 7:369-372 (2001)

<sup>2</sup> Hanan et al., "Inhibitory Effect of Monoclonal Antibodies on Alzheimer's  $\beta$ -Amyloid Peptide Aggregation", *Amyloid: Int. J. Exp. Clin. Invest.*, 3:130-133 (1996)

<sup>3</sup> Bard et al., "Peripherally Administered Antibodies Against Amyloid  $\beta$ -Peptide Enter the Central Nervous System and Reduce Pathology in a Mouse Model of Alzheimer Disease", *Nature Medicine*, 6:916-919 (2000)

<sup>4</sup> Johnson-Wood et al., "Amyloid Precursor Protein Processing and A $\beta_{42}$  Deposition in a Transgenic Mouse Model of Alzheimer Disease", *Proc. Natl. Acad. Sci. USA*, 94:1550-1555 (1997)

<sup>5</sup> Bard et al., "Epitope and Isotype Specificities of Antibodies to  $\beta$ -Amyloid Peptide for Protection Against Alzheimer's Disease-like Neuropathology", *Proc. Natl. Acad. Sci. USA*, 100:2023-2028 (2003)

<sup>6</sup> Solomon et al., "Monoclonal Antibodies Inhibit *in vitro* Fibrillar Aggregation of the Alzheimer  $\beta$ -Amyloid Peptide", *Proc. Natl. Acad. Sci. USA*, 93:452-455 (1996)

<sup>7</sup> Solomon et al., "Disaggregation of Alzheimer  $\beta$ -Amyloid by Site-Directed mAb", *Proc. Natl. Acad. Sci. USA*, 94:4109-4112 (1997)

<sup>8</sup> Solomon et al., "The Amino Terminus of the  $\beta$ -Amyloid Peptide Contains an Essential Epitope for Maintaining its Solubility", in *Progress in Alzheimer's and Parkinson's Diseases*, Fisher et al., ed., Plenum Press, New York, 205-211 (1998)

<sup>9</sup> DeMattos et al., "Peripheral Anti-A $\beta$  Antibody Alters CNS and Plasma A $\beta$  Clearance and Decreases Brain A $\beta$  Burden in a Mouse Model of Alzheimer's Disease", *Proc. Natl. Acad. Sci. USA*, 98:88-90-8855 (2001)

<sup>10</sup> Frenkel et al., "High Affinity Binding of Monoclonal Antibodies to the Sequential Epitope EFRH of  $\beta$ -Amyloid Peptide is Essential for Modulation of Fibrillar Aggregation", *Journal of Neuroimmunology*, 95:136-142 (1999)

<sup>11</sup> Schenk, US 6,761,888 – Table 16 (col 63)